Advances in the Clinical Management of Cardiac Arrest

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ABSTRACT

Cardiac arrest constitutes an extremely life-threatening condition that inevitably and promptly results in death if left untreated. Cardiac arrest outcomes still remain very poor, especially when the presenting cardiac rhythm is nonshockable. Important, recent, clinical research has focused on the quality of cardiopulmonary resuscitation (CPR), the mechanical augmentation of the circulation during CPR, CPR drugs, and therapeutic hypothermia. Chest compression depth of at least 5 cm increases the probability of neurologically favorable survival. Despite initially promising results, a large effectiveness study failed to confirm the efficacy of the mechanical augmentation of the circulation. Epinephrine has finally been shown to slightly improve functional outcome after out-of-hospital cardiac arrest, especially when given early. In a recent, in-hospital study of 268 patients, the addition of vasopressin and methylprednisolone during CPR and the administration of hydrocortisone in postresuscitation shock improved functional outcome after vasopressor-requiring cardiac arrest; however, corticosteroid efficacy still needs to be separately confirmed in a large, international trial. Lastly, preliminary human data may support the conduct of high quality trials evaluating the efficacy of beta adrenergic antagonists in shockable cardiac arrest, and nitrates may warrant evaluation in the clinical setting. The purpose of this paper is to review these potentially important advances in the management of cardiac arrest.

INTRODUCTION

New out-of-hospital and in-hospital cardiac arrest statistics sourced from the Resuscitation Outcomes Consortium Cardiac Registry and Get With The Guidelines® - Resuscitation data show that the incidence of cardiac arrest with any initial rhythm is not decreasing, despite recent advances in preventive medicine and interventional therapeutic strategies. As for in-hospital cardiac arrest, a study published in 2011, concluded that its incidence may actually be increasing. This is important for understanding the burden of in-hospital cardiac arrest and developing strategies to improve care for hospitalized patients.

A large registry study in the United States showed no significant change in survival to discharge among elderly, hospitalized patients treated with cardiopulmonary resuscitation (CPR) for cardiac arrest from 1992 to 2005. However, a more recent registry study indicates that both survival to hospital discharge and neurological outcome im-

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KEY WORDS: cardiac arrest; out-of-hospital cardiac arrest; cardiopulmonary resuscitation; epinephrine

ABBREVIATIONS
AED = automated external defibrillators
ALS = advanced life support
BLS = basic life support
COCPR = chest compression only CPR
CPP = coronary perfusion pressure
CPR = cardiopulmonary resuscitation
ICU = intensive care unit
ITD = impedance threshold device
NO = nitric oxide
OHCA = out-of-hospital arrest
ROSC = return of spontaneous circulation
VF = ventricular fibrillation
VSE = vasopressin-steroids epinephrine
VT = ventricular tachycardia

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Manuscript received December 30, 2013; Revised manuscript received March 15, 2014; Accepted March 24, 2014

Conflict of Interest: none declared
proved substantially within 2000-2009.\textsuperscript{4} Still, rates of survival to hospital discharge with favorable neurological outcome remain low, i.e. approximately 16\% in 2009; pooled data from vasopressor-requiring and non-vasopressor-requiring cardiac arrest.\textsuperscript{4} Thus, further research aimed at improving survival and neurological recovery of cardiac arrest patients is considered as imperative.

Cardiac arrest etiology encompasses a variety of cardiac and noncardiac underlying pathologies. Also, cardiac arrest can occur under different circumstances (e.g. in the presence or absence of witnesses), and settings (e.g. out-of-hospital or in-hospital). This heterogeneity suggests that a single approach to resuscitation may be unrealistic; however, a core bundle of actions results in a universal strategy for achieving successful resuscitation. These actions are termed as the links in the “Chain of Survival”.

The purpose of the current article is to review recent, clinical evidence-based advances in treating patients with cardiac arrest from practices of basic life support (BLS) and advanced life support (ALS) to the post-resuscitation phase in the intensive care unit.

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**KEY CHANGES AND CONTINUED POINTS OF EMPHASIS FROM THE 2005 BLS GUIDELINES**

Prompt recognition of cardiac arrest and action by the rescuer continue to be priorities for the 2010 American Heart Association (AHA) Guidelines for CPR and emergency cardiovascular care.\textsuperscript{4} Rescuers should start CPR immediately if the adult victim is unresponsive and not breathing or only gasping. The “look, listen, and feel” for breathing is no longer recommended. Authors emphasize on uninterrupted (interruptions of less than 10 seconds) and efficient chest compressions. Compressions take priority over airway and breathing, due to the fact that the majority of cardiac arrests in adults result from a primary cardiac cause and thus the major problem is that oxygen delivery to the heart and brain is limited by blood flow rather than by arterial oxygen content.\textsuperscript{6,7} CPR sequence has now changed to Circulation-Airway-Breathing. Guideline experts advise on pushing hard (at least 50 mm) and fast (rate: 100/min), while still allowing full recoil of the chest during decompression. Moreover, experts advise against “excessive ventilation”. The compression to ventilator ratio is 30:2, and when an artificial airway is established, 1-second-lasting breaths (rate: 8-10/min), and asynchronous with compressions are considered as adequate. While positive-pressure ventilation has been a mainstay of CPR, it has recently come under scrutiny because of the potential for the increased intrathoracic pressure’s impeding of the venous return to the heart.

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**CIRCULATORY SUPPORT - CHEST COMPRESSIONS - FIRST PRIORITY**

The “Hands-Only CPR” campaign is now being led by AHA across the United States. There are multiple reasons “chest compression only CPR” (COCPR) might have advantages over conventional CPR. These include the rapid deterioration of forward blood flow that occurs during an even brief interruption of chest compressions,\textsuperscript{8,9} the long ramp-up time to return to adequate blood flow after resuming chest compressions,\textsuperscript{8,9} the reduction in cardiac venous return during positive pressure ventilation,\textsuperscript{10} the complexity of conventional CPR,\textsuperscript{11,12} the significant time required to administer the artificial breaths,\textsuperscript{12-14}\textsuperscript{12-14} and the critical importance of cerebral and coronary circulation during cardiac arrest.\textsuperscript{8,9,15,16}

An increase in the rate of bystanders’ willingness to perform COCPR has been observed. A recent study has evaluated the rate of bystander CPR, as well as survival to hospital discharge, when COCPR has been performed.\textsuperscript{17} This prospective, observational, cohort analysis included 4415 patients who experienced out of hospital cardiac arrest of presumed cardiac etiology. There was a significant difference in good neurological recovery (cerebral performance category score of 1 or 2) between the COCPR group (62/814; 7.6\%; 95\% confidence interval -CI, 5.8\%-9.4\%) and the conventional CPR group (34/651; 5.2\%; 95\% CI, 3.5\%-6.9\%) (P < 0.001).\textsuperscript{16} Furthermore, the largest of the COCPR vs conventional CPR studies,\textsuperscript{16} also found a statistically significant increase in neurologically intact survival with COCPR (18.9\% vs. 13.5\%, P = 0.03). COCPR should not be preferred in victims of asphyxial cardiac arrest (e.g. in the setting of drowning), as in such cases, the prompt reversal of the hypoxemia through ventilation is critical for the restoration of spontaneous circulation (ROSC) and the achievement of a favorable functional outcome.\textsuperscript{19,20}

A coronary perfusion pressure (CPP) of at least 15 mmHg is required to achieve ROSC.\textsuperscript{5} Several authors suggest that chest compressions of 38–51 mm are not deep enough for ROSC.\textsuperscript{21-24} Finally, several reports demonstrate that chest compressions deeper than 51 mm are associated with improved short term outcomes.\textsuperscript{25-28} This chest compression depth is also recommended by the current Guidelines.\textsuperscript{29,30}

In a recent analysis,\textsuperscript{31} the authors evaluated whether the depth of chest compressions provided by prehospital rescuers is independently associated with survival and favorable functional outcome. This study included 593 adults with out-of-hospital arrest (OHCA) of presumed cardiac etiology. Chest compression quality was measured during resuscitation, including minute-by-minute rate and depth data. Interruptions in compressions were assessed using the chest compression fraction, i.e. the percentage of time compressions were performed throughout the entire resuscitation procedure. Chest compression rate was similar for survivors 113.5 (95\% CI 108.5–118.6) and non-survivors 112.7 (95\% CI 110.9–114.4).
Chest compression depth was significantly greater in survivors (53.6 mm; 95% CI 50.5–56.7) than in non-survivors (48.8 mm; 95% CI 47.6–50.0). Notably, the median percentage of chest compressions of at least 51 mm was 64.0% (95% CI 47.0–81.0) for survivors and 45.0% (95% CI 39.6–50.4) for non-survivors.

The odds of survival increased by 29% for every 5 mm increase in mean chest compression depth (adjusted odds ratio - OR = 1.29; 95% CI 1.00–1.65). Likewise, a favorable functional outcome had 30% better odds for each 5 mm increase in chest compression depth (adjusted OR = 1.30; 95% CI 1.00–1.70). Furthermore, the odds of survival to hospital discharge and favorable functional outcome increased by 21% for each 10% increment of chest compressions of at least 51 mm. In addition, survivors were more likely to have been treated with mean chest compression depth of at least 51 mm as compared with non-survivors (64% vs. 45%). However, while deeper chest compressions were positively associated with improved outcomes, the optimal chest compression depth remains unknown.

DEFIBRILLATION

Defibrillation is the application of a preset electrical current across the myocardium to cause synchronous depolarization of the cardiac muscle. In ventricular fibrillation (VF) / ventricular tachycardia (VT) cardiac arrest, the goal of defibrillation is to restore an organized cardiac rhythm (ideally normal sinus rhythm) that will result in ROSC. Defibrillators work as capacitors discharging their stored energy through a circuit that includes the patient’s heart. Optimal, monophasic and biphasic defibrillator current (I) ranges within 30-40 A and 15-20 A, respectively.32 Current duration (t) ranges within 10-20 ms, and the adult patient transthoracic impedance (R) usually ranges within 70-80 Ω.32 The energy delivered to the patient is proportional to the stored charge (Q) and the capacitor voltage (V):

\[ \text{Energy} = \frac{1}{2} \cdot Q \cdot V = \frac{1}{2} \cdot (I \cdot t) \cdot (I \cdot R) = \frac{1}{2} \cdot I^2 \cdot R \cdot t. \]

For monophasic defibrillators, the recommended energy level is 360 J. For biphasic defibrillators, the initial energy level should be at least 150 J.32 The sum of the defibrillator’s electrode areas should be at least 150 cm²;33 and a force of 8 kg should be applied on them, in order to minimize R and thus maximize current flow through the heart.32

The use of automated external defibrillators (AEDs) has revolutionized the capability of timely delivery of defibrillation to VF/VT victims. The availability of AEDs is currently recommended for both public, out-of-hospital and non-monitored, in-hospital settings.32 The safety and effectiveness of AEDs with respect to prompt defibrillation and survival is supported by a considerable amount of previously published data.34 Nevertheless, in a recent retrospective analysis of OHCA the use of AEDs by bystanders was quite infrequent, i.e. an AED was retrieved and used successfully before ambulance arrival in less than 2% of 1035 OHCA cases.35

Whenever the first shock is preceded by CPR, the delay between chest compression interruption and shock delivery (pre-shock pause) should be kept to less than 5 s, and chest compressions should be resumed immediately after the shock.32 There is currently insufficient data to support or refute a pre-specified period of 2-3 min of pre-shock CPR in the out-of-hospital setting.32 However, regarding in-hospital VF/VT, defibrillation should be administered as soon as possible. Defibrillation in the (early) electrical phase (i.e. within 1-3 min of VF/VT onset) has a high probability of success that may exceed 90%, especially when a biphasic waveform is used.32 Patients experiencing VF/VT in the cardiac catheterization laboratory or following cardiac surgery may be treated with three quick successive (stacked) shocks.32 In all other cases of in-hospital or out-of-hospital VF/VT, shocks should be interspersed with 2-min periods of chest compressions and vasopressors and antiarrhythmics should be given after the third shock.32

The optimal energy for defibrillation is that which achieves VF/VT termination and ROSC whilst causing the minimum of myocardial damage.32,36 Biphasic vs monophasic waveforms are more effective at terminating ventricular arrhythmias at lower energy levels, and have greater first shock efficacy.32,37,39 However, the potential superiority of biphasic waveforms with respect to neurologically favourable survival still remains to be demonstrated.32

Multiple clinical studies suggest that it is possible to predict the success of defibrillation from VF waveform analysis with varying reliability.40 However, a recent, multicenter study comparing a VF waveform analysis algorithm for identification of VF unlike to respond to immediate defibrillation with a standard shock-first protocol failed to show any waveform analysis-associated improvement in survival to hospital discharge.41 Consequently, the value of VF waveform analysis remains uncertain.40

MECHANICAL AUGMENTATION OF CIRCULATION

Over the past 25 years, a variety of alternatives to conventional, manual CPR have been developed in an effort to enhance perfusion during attempted resuscitation from cardiac arrest and to improve survival. In the 2010 AHA guidelines,42 the authors warn that usage of such devices may delay or interrupt CPR. They claim that these devices typically require more personnel, training, and equipment, or they apply to a specific setting. In recent bibliography, there is a lot of debate about active compression-decompression (ACD-CPR) CPR, applied in conjunction with the impedance threshold device (ITD).

ACD-CPR is performed with a device that includes a suction cup to actively lift the anterior chest during decompression
The application of external negative suction during the decompression phase of CPR creates negative intrathoracic pressure, thus potentially enhancing venous return to the heart.

The ITD is a pressure-sensitive valve that is attached to an endotracheal tube, supraglottic airway, or face mask (Fig. 2). The ITD limits air entry into the lungs during the decompression phase of CPR, creating negative intrathoracic pressure and improving venous return to the heart and cardiac output during CPR. It does so without impeding positive pressure ventilation or passive exhalation. Studies of the mechanisms involved in animals and humans provide the physiological underpinnings for “the other side of breathing”: to increase circulation to the heart and brain. A review article on the effects of the respiratory pump to improve vital organ perfusion by ITD, described studies that focused on the fundamental relationship between the generation of negative intrathoracic pressure during inspiration through a low-level of resistance created by an ITD and the physiologic effects of a respiratory pump. A decrease in intrathoracic pressure during inspiration through a fixed resistance resulting in an intrathoracic pressure of -7 cmH₂O has multiple physiological benefits, including enhanced venous return, cardiac stroke volume and aortic blood pressure, lower intracranial pressure; resetting of the cardiac baroreflex, elevated cerebral blood flow oscillations, and an increased tissue blood flow/pressure gradient.

Already in the early 2000s, some studies reported that the combination of ACD-CPR and ITD, when performed correctly, results in an increase of more than 50% in coronary perfusion pressure, and an improved 24-hour survival and neurological function in cardiac arrest patients. The results of a presumed cardiac-cause OHCA, multicenter, randomized, unblinded trial, demonstrated a relative increase of 53% in survival to hospital discharge with favorable neurologic outcome, when a combination of ACD-CPR and ITD was applied compared with standard CPR. One year after OHCA, survival was still higher (by more than 50%) in the intervention group and there were similar proportions of restoration of neurologic function in both groups. There was no significant difference in the overall major adverse event rates between groups. However, pulmonary edema was more common in the intervention group. The aforementioned study further demonstrated that it is practicable to teach and implement ACD-CPR and ITD skills in urban, suburban, and rural Emergency Service environments.

Opposed to this study is a large effectiveness trial, which did not confirm a survival advantage with the use of an ITD during standard CPR in patients with nontraumatic OHCA. The authors suggested that the neutral results could have been due to the fact that the ITD may not generate or its use by the Emergency Service systems couldn’t recreate the proposed physiological benefits. Another possible explanation was that the ITD did generate the physiological effects seen in experimental studies but couldn’t change clinical outcomes.
EPINEPHRINE

The primary goal of pharmacologic therapy during cardiac arrest is to facilitate restoration and maintenance of a perfusing, spontaneous rhythm. Toward this goal, ALS drug therapy during CPR is often associated with increased rates of ROSC and survival to hospital admission but not increased rates of long-term survival with good neurological outcome.

One study randomized patients to intravenous or no intravenous medications during OHCA.63 The study demonstrated higher rates of ROSC in the intravenous vs the no intravenous group (40% vs 25%; OR 1.99; 95% CI 1.48 to 2.67), but there was no significant difference in the survival to hospital discharge (10.5% vs. 9.2%; OR 1.16; 95% CI 0.74 to 1.82), or the survival to hospital discharge with favorable neurological outcome (9.8% vs. 8.1%; OR 1.24; 95% CI 0.77 to 1.98). Among patients randomized to intravenous access, 79% received epinephrine, 46% atropine and 17% amiodarone, and it was not possible to determine the efficacy of these drugs (either individually or in combination) with respect to the reported outcomes. Furthermore, as the intervention could not be blinded, the potential for paramedics to respond differently, particularly when knowing that patients randomized to the no intravenous access group would have drug therapy withheld, may have introduced a bias. While the investigators identified no difference in a number of CPR quality measures across both study arms in the 75% of events assessed, the potential bias inherent with non-blinding could not be ruled out.

Accordingly, the first randomized, double-blind, placebo-controlled trial of epinephrine in OHCA reported that epinephrine increases ROSC but not survival to hospital discharge.52 A recent review of epinephrine in OHCA54 included another four prospective cohort studies,55-58 one retrospective cohort study,59 one survival analysis,60 and one case control study.61 The authors of the review reported on the paucity of supporting evidence for the use of epinephrine in OHCA. Several experts have recently suggested that new, large, randomized, controlled trials may be needed to reliably establish the effect of epinephrine on the survival to hospital discharge and neurological outcome.

A recent, retrospective analysis of prospectively collected, population-based data (n=49165 adults with witnessed OHCA of cardiac origin) showed that epinephrine administration within 10 min of collapse was associated with improved survival to hospital discharge (OR 1.73; 95% CI 1.46 to 2.04) and good neurological outcome (OR 1.39, 95% CI 1.08 to 1.78).62 Epinephrine effectiveness has been now reconfirmed by a large propensity analysis showing a slightly improved, neurologically favorable survival with epinephrine use vs. no use (0.7% vs. 0.4%; OR 1.57 95% CI 1.04 to 2.37) in 9058 pairs of patients with nonshockable OHCA.63 Another recent review of 20909 in-hospital cardiac arrest events showed that increasing the epinephrine dosing interval from the guideline-recommended of 3-5 min to 6-10 min was associated with improved survival to hospital discharge (adjusted ORs 1.30-2.17; 95% CIs 1.02-1.62 to 1.65-2.92).64 Consequently, future trials should also determine the optimal timing of epinephrine administration (initial and dosing interval) as well.

VASOPRESSIN AND STEROIDS

In a previous, single-center, randomized, controlled study,65 combined vasopressin-epinephrine during CPR and corticosteroid supplementation during and after CPR vs. epinephrine alone during CPR and no steroids resulted in improved overall survival to hospital discharge. Patients in the vasopressin-steroids epinephrine (VSE) group had more frequent ROSC, and attenuated postresuscitation systemic inflammatory response66,67 and organ dysfunction.68 This preliminary study could not reliably assess VSE efficacy with respect to neurologically favorable survival to hospital discharge. The current authors addressed this question with a 3-center study of vasopressor-requiring, in-hospital cardiac arrest;69 the study protocol was identical to that of the preliminary study.65 This randomized, controlled trial included 268 consecutive patients with cardiac arrest requiring epinephrine according to resuscitation guidelines (from 364 patients assessed for eligibility). Patients received either vasopressin (20 IU/CPR cycle) plus epinephrine (1 mg/CPR cycle; cycle duration approximately 3 min) (VSE group, n = 130) or saline placebo plus epinephrine (1 mg/CPR cycle; cycle duration approximately 3 min) (control group, n = 138) for the first 5 CPR cycles after randomization, followed by additional epinephrine if needed. During the first CPR cycle after randomization, patients in the VSE group received 40 mg of methylprednisolone and patients in the control group received saline placebo. Shock after resuscitation was treated with stress-dose hydrocortisone (VSE group) or saline placebo (control group; see below).

Patients in the VSE group vs. patients in the control group had higher probability for ROSC for 20 minutes or longer (83.9% vs 65.9%; OR 2.98; 95% CI 1.39 to 6.40) and survival to hospital discharge with good neurological outcome (13.9% vs 5.1%; OR 3.28; 95% CI 1.17 to 9.20). Results on the postresuscitation shock subgroup were also favorable for the VSE combination (see below). Table 1 displays important peri-arrest characteristics and variables of the pooled study population65,66 these data are presented mainly to enable readers to independently assess the baseline status of the 2 pooled groups. Figure 3 displays the pooled outcome data from the total of the 368 studied patients.

Both VSE studies exhibit limitations: results refer only to in-hospital cardiac arrest, there was no assessment of CPR quality, the VSE protocol did not allow a precise determination of the relative contribution of vasopressin and steroids to
TABLE 1. Important baseline and peri-arrest characteristics of the pooled study populations of references 65 and 67.

<table>
<thead>
<tr>
<th>Baseline Characteristic or Per-arrest Variable</th>
<th>Control group (n = 190)</th>
<th>VSE Group (n = 178)</th>
<th>P value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - years</td>
<td>64.6 ± 18.5</td>
<td>63.8 ± 17.6</td>
<td></td>
</tr>
<tr>
<td>Male gender - no. (%)</td>
<td>117 (61.6)</td>
<td>125 (70.2)</td>
<td></td>
</tr>
<tr>
<td>Hypertension - no. (%)</td>
<td>110 (57.9)</td>
<td>95 (53.4)</td>
<td></td>
</tr>
<tr>
<td>Coronary disease - no. (%)</td>
<td>62 (32.6)</td>
<td>65 (36.5)</td>
<td></td>
</tr>
<tr>
<td>Diabetes - no. (%)</td>
<td>45 (23.7)</td>
<td>48 (27.0)</td>
<td></td>
</tr>
<tr>
<td>Hypotension(^b)</td>
<td>70 (36.8)</td>
<td>84 (47.2)</td>
<td></td>
</tr>
<tr>
<td>Respiratory(^c)</td>
<td>71 (37.4)</td>
<td>52 (29.2)</td>
<td></td>
</tr>
<tr>
<td>Myocardial ischemia(^d)</td>
<td>36 (19.0)</td>
<td>42 (23.6)</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>27 (14.2)</td>
<td>13 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Lethal Arrhythmia</td>
<td>14 (7.4)</td>
<td>10 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.1)</td>
<td>6 (3.4)</td>
<td></td>
</tr>
<tr>
<td>VF/pulseless VT – no. (%)</td>
<td>30 (15.8)</td>
<td>29 (16.3)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Asystole – no. (%)</td>
<td>128 (67.4)</td>
<td>113 (63.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>PEA – no. (%)(^e)</td>
<td>32 (16.8)</td>
<td>36 (20.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>Witnessed arrest - no. (%)</td>
<td>169 (89.0)</td>
<td>159 (89.3)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td><strong>Location of cardiac arrest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital ward - no. (%)</td>
<td>83 (43.7)</td>
<td>78 (43.8)</td>
<td>0.98</td>
</tr>
<tr>
<td>Intensive care area - no. (%)</td>
<td>67 (35.3)</td>
<td>65 (36.5)</td>
<td></td>
</tr>
<tr>
<td>Emergency department - no. (%)</td>
<td>31 (16.3)</td>
<td>29 (16.3)</td>
<td></td>
</tr>
<tr>
<td>Operating room - no. (%)</td>
<td>9 (4.7)</td>
<td>6 (3.4)</td>
<td></td>
</tr>
<tr>
<td><strong>ALS duration, median (IQR) - min</strong></td>
<td>20 (10-30)</td>
<td>14 (7-24)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Time to ALS initiation from emergency call - median (IQR; range) - min</strong></td>
<td>1 (1-2; 0-4)(^d)</td>
<td>1 (1-2; 0-4)(^d)</td>
<td>0.16</td>
</tr>
<tr>
<td>Epinephrine dose, median (IQR) - mg</td>
<td>5 (3-9)</td>
<td>4 (2-6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Rate of ROSC ≥20 min, after second vasopressor dose - no. (%)</td>
<td>33 (17.4)</td>
<td>50 (28.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Overall rate of ROSC – no (%)</td>
<td>118 (62.1)</td>
<td>148 (83.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^a\) Baseline characteristics were not compared between the 2 groups. \(^b\) Imbalance potentially favoring control group outcomes. \(^c\) Imbalance potentially favoring VSE group outcomes. \(^d\) Data available from 171 patients. \(^e\) Data available from 159 patients.

The high mortality rate of patients who initially achieve ROSC after cardiac arrest can be attributed to a pathophysiological process that involves multiple organs. Although prolonged, whole-body ischemia initially causes global tissue and...
CARDIAC ARREST MANAGEMENT

Organ injury, while additional damage occurs during and after reperfusion. The unique features of post–cardiac arrest pathophysiology are often superimposed on the disease or injury that caused the cardiac arrest, as well as the underlying comorbidities. Therapies that focus on individual organs may compromise other injured organ systems. The four key components of post-cardiac arrest syndrome are 1) post–cardiac arrest brain injury, 2) post–cardiac arrest myocardial dysfunction, 3) ischemia/reperfusion-triggered, systemic inflammatory response, and 4) persistent underlying pathology.

The recognition of the importance of post resuscitation care on long term survival and favorable neurological outcome led to the addition of a fifth ring to the chain of survival, termed “post-resuscitation care”.

2010 AHA GUIDELINES FOR POST-RESUSCITATION CARE – OVERVIEW

There is paucity of data reported from the post-arrest, in-hospital phase, and no generally accepted, evidence-based protocol exists, other than brain protection-oriented intensive care.

The AHA 2010 guidelines suggest a multiple system approach.

Although 100% oxygen may have been used during initial resuscitation, providers should titrate inspired oxygen fraction (FiO₂) as soon as possible to the lowest level required, ensuring an adequate arterial oxygen content and avoiding oxygen toxicity. The optimal FiO₂ is under debate. Animal data suggest that ventilation with 100% oxygen (generating a PaO₂ of more than 350 mm Hg at 15 to 60 minutes after ROSC) increases brain lipid peroxidation, neuronal metabolic dysfunction and degeneration, and worsens short-term functional outcome when compared with ventilation with room air or an FiO₂ titrated to a pulse oximeter reading of 94% to 96%. Physicians should try to achieve an arterial oxygen saturation of at least 94%, for all patients after ROSC. Hyperventilation should be avoided for its adverse hemodynamic effects, as well as for the potential vasoconstriction that low PaCO₂ can cause in the cerebral circulation. Minute ventilation should be titrated targeting an end-tidal CO₂ of 35 to 40 mmHg or a PaCO₂ of 40 to 45 mmHg. Although human studies have not established ideal targets for blood pressure or blood oxygenation, a mean arterial pressure of at least 65 mmHg and a central-venous oxygen saturation of at least 70% are generally considered as reasonable goals. Vasoactive drug infusions may be considered in order to achieve this goal.

Hyperglycemia or hypoglycemia can have detrimental effects on survival and neurological recovery. The optimum blood glucose concentration and interventional strategy to manage blood glucose in the post–cardiac arrest period is unknown. Moderate glycemic control (144 to 180 mg/dL) seems reasonable in adult patients with ROSC after cardiac arrest.

THERAPEUTIC HYPOTHERMIA

For protection of the brain and other organs, hypothermia is a helpful therapeutic approach in patients who remain comatose (usually defined as a lack of meaningful response to verbal commands) after ROSC. Questions remain about specific indications and populations, timing and duration of therapy, and methods for induction, maintenance, and subsequent reversal of hypothermia.

The recommended temperature of 32°C to 34°C has been extrapolated from experiments in animals; however, similar results have been observed with milder cooling. Although a Cochrane review supported these guidelines, some investigators have suggested a need for additional trials to confirm or refute this treatment strategy.

The use of therapeutic hypothermia is supported by the results of 2 prior, randomized, controlled trials of OHCA
with a shockable rhythm that showed improved neurological outcomes in hypothermia-treated patients. In both trials, there were no pre-specified temperature control measures for control patients. Mild hypothermia (32-34°C) for 12 to 24 hours improved neurological recovery and survival, despite delays of 4 to 8 hours in achieving goal temperatures.

Neutral results on hypothermia were reported by the investigators of a recent, international, multicenter, randomized, controlled trial. This trial compared a target body temperature of 33°C with one of 36°C in patients resuscitated from OHCA of presumed cardiac cause. Hypothermia was induced as rapidly as possible with the use of ice-cold fluids, ice packs, and intravenous or surface temperature-management devices at the discretion of the attending physician. The time interval between ROSC and induction of hypothermia was 20 to 240 min. There were no significant differences between the two groups in overall mortality at the end of the trial or in the composite outcome of poor neurologic function or death at 180 days.

A difference between the recent trial and the earlier trials is that the natural trajectory of temperature evolution was not allowed in either group. Indeed, temperature was actively controlled during the intervention period in both groups and fever was prevented during the first 3 days after cardiac arrest. As in the earlier trials, the investigators did enroll patients with OHCA of presumed cardiac cause, but the sample was larger and approximately 20% of participants had nonshockable rhythms.

Other published studies involving patients with cardiac arrest who were admitted to the ICU have shown baseline characteristics and mortality that are in keeping with the findings of the recent, large trial. The mortality in both groups of this trial was lower than that in the control group of the Hypothermia after Cardiac Arrest trial. This can be attributed to the fact that both prehospital and critical care have improved during the past decade. Fever frequently develops after ROSC because of a systemic inflammatory response. Nevertheless, it is important to acknowledge that there may be a clinically relevant benefit of controlling the body temperature at 36°C, instead of allowing fever to develop in patients who have been resuscitated after cardiac arrest.

Bernard et al. conducted an investigation in 2010 inducing hypothermia in the field or after hospital admission in patients resuscitated from out of hospital arrest presenting with a shockable rhythm. No benefit was observed. The recent, large randomized trial by Kim et al found that prehospital, rapid infusion of up to 2 L of cold (4°C) normal saline did induce mild hypothermia, approximately 60 min faster than standard care, but did not improve survival or neurological status at discharge after resuscitation from prehospital, shockable (VF) or nonshockable (non VF) cardiac arrest. The intervention was associated with a significantly increased incidence of early re-arrest, and pulmonary edema/diuretic use (in the Emergency Department).

### Corticosteroids

Corticosteroids are a class of chemicals involved in a wide range of physiological processes, including stress response, immune response and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.

Preceding retrospective studies with inherent methodological limitations did not support the use of low-dose corticosteroids during and after CPR. However, more recent laboratory data and clinical results are consistent with a possible, low-dose corticosteroid-associated, benefit in cardiac arrest, especially in patients with postresuscitation shock. Such potential benefit can be explained mainly by the hemodynamic and anti-inflammatory properties of hydrocortisone.

Cardioprotective effects of glucocorticoids in the acute setting of myocardial ischemia/reperfusion have been shown experimentally with regard to structural and functional myocardial damage. Also, a meta-analysis of human data from 11 controlled trials suggested a possible mortality benefit for corticosteroid treatment of myocardial infarction.

Glucocorticoids attenuate leukocyte/endothelium interactions as well as the generation and release of inflammatory cytokines and mediators. The Surviving Sepsis Campaign guidelines 2012 for the management of severe sepsis and septic shock suggest stress-dose hydrocortisone therapy (daily dose: 200 mg) only for patients who are poorly responsive to fluid and vasopressor therapy. Likewise, in cardiac arrest patients, treatment-refractory shock is a common post-ROSC complication. Furthermore, postresuscitation shock is frequently partly due to a post-arrest adrenal insufficiency or dysfunction, which in turn constitutes an independent predictor of mortality at one week after resuscitation.

The mechanisms underlying the post-cardiac arrest syndrome involve a whole body ischemia and reperfusion that triggers a systemic inflammatory response. Overall, the high levels of circulating cytokines, the presence of endotoxin in plasma, and the dysregulated production of cytokines found in cardiac arrest patients resemble the immunological profile found in patients with sepsis. A recent, observational OHCA study found a 38% incidence of bacteremia upon presentation to the Emergency Department. A similar incidence of cardiac arrest-associated bacteremia has been previously reported by others as well. Consequently, actual septic insults may frequently contribute to the development and the severity of the postresuscitation hemodynamic instability. This fact, in conjunction with the lower absolute serum cortisol levels previously documented in patients with poor CPR/postresuscitation outcomes, the previously reported, strong, negative correlation between
cortisol levels and “no-flow” time, and the frequently severe postresuscitation, hemodynamic instability that does not adequately respond to fluid and vasopressor therapy, provides a robust framework for the rationale of glucocorticoid supplementation in the peri-arrest and postresuscitation period.

In our recent in-hospital cardiac arrest studies, we administered 40 mg of methylprednisolone during CPR (in combination with vasopressin/epinephrine – see also above), and stress dose hydrocortisone (300 mg/day for a maximum of 7 days followed by gradual taper) to patients fulfilling a clearly defined criterion for postresuscitation shock. Patients with evidence of myocardial infarction received a 3-day course of stress dose hydrocortisone (followed by gradual taper), in order to prevent any potential retardation of infarct healing. Compared to control, the postresuscitation shock subgroups of the VSE groups had improved post-arrest hemodynamics and central venous oxygen saturation, post-arrest cytokine levels and organ/system function, and survival to hospital discharge with favorable neurological recovery. Accordingly, pooled subgroup results show more VSE patients (23/103, 22.3%) than control patients (6/88, 6.8%) with good functional outcome (hazard ratio for death during follow-up or severe cerebral disability/vegetative state: 0.64; 95% confidence interval 0.46 to 0.88; \( P = 0.006 \)).

As already mentioned above, due to the VSE combination, we could not separately assess glucocorticoid efficacy. Therefore, a large, multicenter, randomized, placebo-controlled evaluation of stress-dose glucocorticoid supplementation in cardiac arrest is still needed. Such a study should provide definitive results on the efficacy, and appropriate dosage and timing of steroid administration. Lastly, although there is no published data suggestive of a glucocorticoid-associated neuroprotection, recent laboratory results suggest that the biosynthetically related estrogens may actually mitigate the effects of global cerebral ischemia.

**BETA ADRENERGIC ANTAGONISTS**

Two small, clinical, prospective human studies tested the effects of beta-blockade against regular therapy in patients presenting with electrical storm. In the intervention group of the first study, sympathetic blockade resulted in a decline in the mean number of VF episodes from over 20 to 2.6 ± 1.7 per day (\( P < 0.01 \)). In contrast, 91% of patients in the control group continued to have VF episodes. At the end of the first year of follow-up, 18/27 patients in the beta blockade group were still alive, compared with 1/22 in the control group. In the other human trial, 42 consecutive patients with electrical storm refractory to regular ALS therapy received intravenous lanidol in increasing doses (starting at 2.5 μg/kg/min; maximum dose was 80 μg/kg/min), subsequently titrated to the minimum infusion rate required for arrhythmia control. The study protocol was ineffective in 9 patients (21%), who died of arrhythmia. From the 33 responders, 21 received carvedilol and 12 were started on bisoprolol, with oral beta-blocker administration immediately after stabilization. Eight of these 33 patients (19%) died afterwards from multiple organ failure or infection, and 25 (60%) survived to hospital discharge.

A recently published review on the use of beta-blockers in cardiac arrest with shockable rhythms concluded that available human studies may point toward a beneficial effect of beta-blockade in patients, which is in accordance with the results from the majority of relevant clinical case reports and animal experimental studies. However, high quality human trials are warranted, in order to reliably evaluate the potential usefulness of the beta-blockers in cardiac arrest. Indeed, beta-blockers may counteract the potentially deleterious beta-adrenergic effects of epinephrine, which may contribute to the postresuscitation myocardial dysfunction and the recurrence of life-threatening arrhythmias.

**OTHER ANTIARRHYTHMIC DRUGS**

Amiodarone affects sodium, potassium, and calcium channels and has alpha and beta adrenergic blocking properties. It can be given as an initial IV bolus of 300 mg to patients with refractory VF/VT cardiac arrest not responsive to CPR, defibrillation (i.e. 3 shocks), and vasopressors. If VF/VT persists after the 4th shock, an additional amiodarone IV bolus of 150 mg may be considered. Amiodarone effectiveness with respect to improved survival to hospital admission of OHCA patients is supported by the results of 2 blinded, randomized, controlled trials. If amiodarone is not available, the sodium channel blocker lidocaine may be given with an initial IV bolus of 1-1.5 mg/kg, followed by additional IV boluses of 0.5-0.75 mg/kg every 5-10 min and up to a total dose of 3 mg/kg. Lastly, IV magnesium sulfate can be given exclusively for the treatment of irregular/polymorphic VT associated with prolonged QT interval.

**NITRATES**

The greatest proportion of in-hospital, post-resuscitation mortality is caused by global ischemic brain injury, whereas both myocardial dysfunction and systemic inflammation predispose to poor neurological outcome. Mechanisms of post-resuscitation brain injury include excito-toxicity, free radical formation, pathological activation of proteases, and cell death signalling. The injurious pathways include disruption of the blood–brain barrier, neuro-inflammation, and delayed neuro-degeneration. Nitrite therapy limits cellular injury and apoptosis after ischemia and reperfusion (I/R). It has been proven to be
cytoprotective in numerous animal models of focal I/R injury, including rodent heart, brain, liver and kidney, canine heart, and primate brain.151-155 Systemic nitrite reduction by ceruloplasmin knockout or dietary nitrate/nitrite elimination increased infarction volume in the liver and heart after experimental ischemia.156,157 These studies indicate that physiological systemic nitrite levels modulate host resilience to ischemia. The established safety of human and animal nitrite dosing158 and its potent effects in limiting major organ injury suggest that nitrite represents an ideal candidate for the treatment of cardiac arrest.

Nitric oxide (NO) is produced from NO synthases (NOS, i.e. NOS1, NOS2, and NOS3). NO exerts a number of effects that would be expected to be beneficial during I/R injury.159 NO is a potent vasodilator which inhibits platelet and leukocyte activation and adhesion, inhibits reactive oxygen species (ROS)-producing enzymes, and directly scavenges ROS.160 Studies using NOS3 knockout mice showed that NOS3 deficiency aggravates I/R injury in the brain and heart,161,162 whereas cardiomyocyte-specific overexpression of NOS3 attenuated postresuscitation myocardial and neurological dysfunction in NOS3-deficient mice.163

Several recent studies are also consistent with a nitrite treatment/NO associated benefit in experimental cardiac arrest.71,73,164-169 Likely mechanisms of brain protection may involve the primary intra-cellular target of NO, i.e. soluble guanylate cyclase,167 or increased levels of neuronal nitrite and S-nitrosothiols.168 The neuroprotective effects of hypothermia seem to be at least partly mediated through enhanced NOS3 signalling.180 Also, inhaled NO (40 ppm) improves neurological outcomes during concurrent use of hypothermia.169

In contrast to NO, NO-donor compounds may induce systemic vasodilation and hypotension, frequently precluding their use in the setting of cardiac arrest-associated hemodynamic instability. On the other hand, inhaled NO is a selective pulmonary vasodilator that does not produce systemic hypotension when inhaled at concentrations of up to 80 ppm in multiple species, including man.170 The absence of systemic vasodilation during NO inhalation is due to the rapid scavenging of NO by hemoglobin in the blood.

Some NO, once inhaled, may escape scavenging by hemoglobin and be converted to relatively stable NO metabolites (e.g., nitrite and S-nitrosothiols) that can regenerate NO in the periphery.171 NO inhalation has been associated with marked increases in the arterial blood concentration of NO metabolites.172 Also, regenerated NO may exert regional vasodilating effects. Indeed, a recent study by Terpolilli et al.173 showed that NO inhalation prevented ischemic brain injury in mice and sheep by selective dilatation of collateral arterioles. The aforementioned, promising, experimental results provide a robust background for a possible, future evaluation of nitrates/NO in the clinical setting.

CONCLUSIONS

Our clinical knowledge and practices with respect to the management of cardiac arrest have substantially improved during the last 10-15 years. This has resulted in significant improvements in the survival with favorable neurological outcome. Furthermore, recent, promising study results may guide future research aimed at establishing definitive evidence for more effective therapeutic approaches during CPR and ALS, as well as during the postresuscitation period.

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